

(19) World Intellectual Property Organization
International Bureau



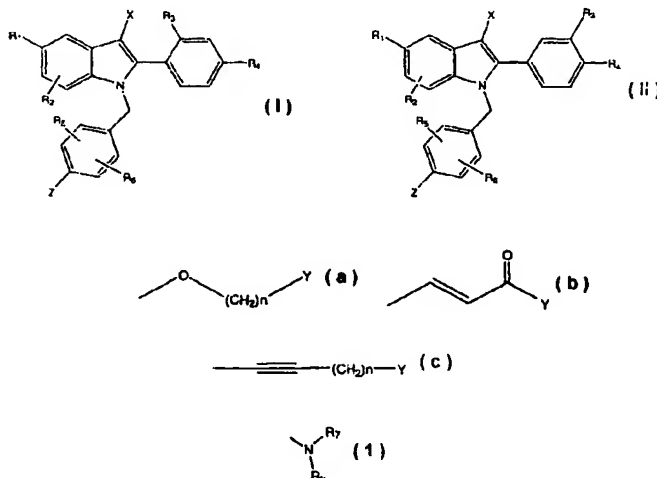
(43) International Publication Date
17 January 2002 (17.01.2002)

PCT

(10) International Publication Number
WO 02/03976 A2

- (51) International Patent Classification⁷: **A61K 31/00**
- (21) International Application Number: PCT/US01/20970
- (22) International Filing Date: 29 June 2001 (29.06.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/216,069 6 July 2000 (06.07.2000) US
60/216,188 6 July 2000 (06.07.2000) US
- (71) Applicant: **AMERICAN HOME PRODUCTS CORPORATION** [US/US]: Five Giralda Farms, Madison, NJ 07940-0874 (US).
- (72) Inventors: **JENKINS, Simon, Nicholas**; 3011 Timothy's Trail, Audubon, PA 19403 (US). **KOMM, Barry, Samuel**; 1122 Cymry Drive, Berwyn, PA 19312 (US). **MILLER, Christopher, Paul**; 72 Meadowbrook Road, Strallford, PA 19087 (US).
- (74) Agents: **MILOWSKY, Arnold, S.**; American Home Products Corporation, Patent Law Department, Five Giralda Farms, Madison, NJ 07940 et al. (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:**
... without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMBINATIONS OF BISPHOSPHONATES, ESTROGENIC AGENTS AND OPTIONALLY ESTROGENS



(57) Abstract: This invention comprises methods of treating bone disorders and lowering blood LDL levels comprising administration of a bisphosphonate, and compound of the formula (I) or (II), wherein Z is a moiety selected from the group of (a), (b), or (c); wherein: R₁ is selected from H, OH or the C₁-C₁₂ alkyl ethers thereof, benzyloxy, or halogen; or C₁-C₄ halogenated ethers including trifluoromethyl ether and trichloromethyl ether; R₂, R₃, R₄, R₅, and R₆ are H, OH or C₁-C₁₂ alkyl ethers thereof, halogens, or C₁-C₄ halogenated ethers, cyano, C₁-C₆ alkyl, or trifluoromethyl, with the proviso that, when R₁ is H, R₂ is not OH; Y is the moiety (1); R₇ and R₈ are alkyl or concatenated together to form an optionally substituted, nitrogen-containing ring; or a pharmaceutically acceptable salt thereof, and optionally an estrogen.

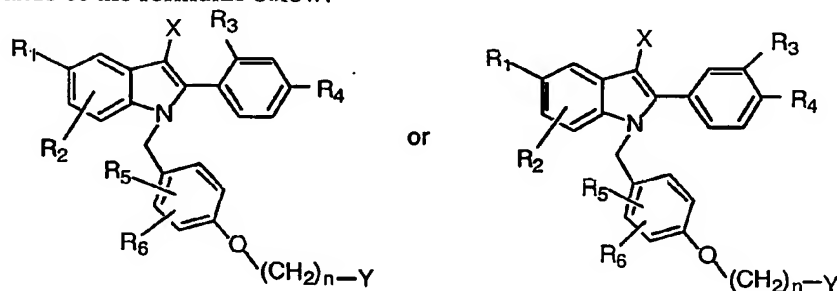
- 1 -

**COMBINATIONS OF BISPHOSPHONATES, ESTROGENIC AGENTS AND
OPTIONALLY ESTROGENS**

5 This invention relates to methods of using substituted indole compounds in the combination with a bisphosphonate and optionally one or more estrogens for strengthening of bone and the treatment, prevention, inhibition or alleviation of bone disorders, including osteoporosis and Paget's disease, and related pharmaceutical compositions and kits.

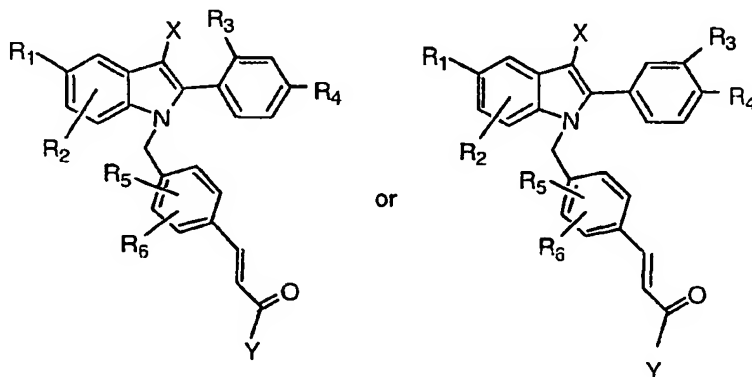
10 **Background of the Invention**

EP 0 802 183 A1 and U.S. Patent No. 5,780,497 describe substituted indole compounds of the formulae below:



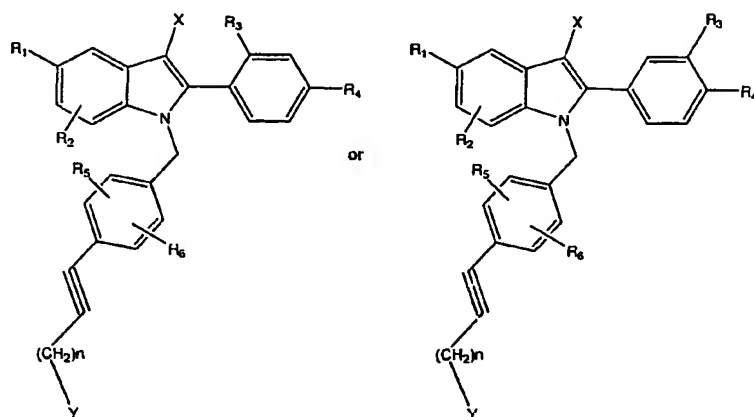
15 as well as their use as estrogenic agents, including the treatment of bone loss, cardiovascular disease, maladies associated with or resulting from the proliferation or abnormal development of endometrial or endometrial-like tissues, and disease states or syndromes associated with estrogen deficiency.

20 EP 0 802 184 A1, published October 22, 1997, describes comparable uses for substituted indole compounds of the formulae below.



- 2 -

Analogous indole compounds having the general structures:



are described in U.S. Patent No. 5,880,137 (Miller et al.).

5

Filipponi P et al: Cyclical clodronate is effective in preventing post-menopausal bone loss: A comparative study with transcutaneous hormone replacement therapy. J Bone Min Res 10:697-703, 1995.

10

Description of the Invention

This invention comprises methods of treating, preventing, alleviating or inhibiting bone disorders, including osteoporosis or Paget's disease in a mammal, preferably in a human, the methods comprising administering to a mammal in need thereof a pharmaceutically effective combination of:

15

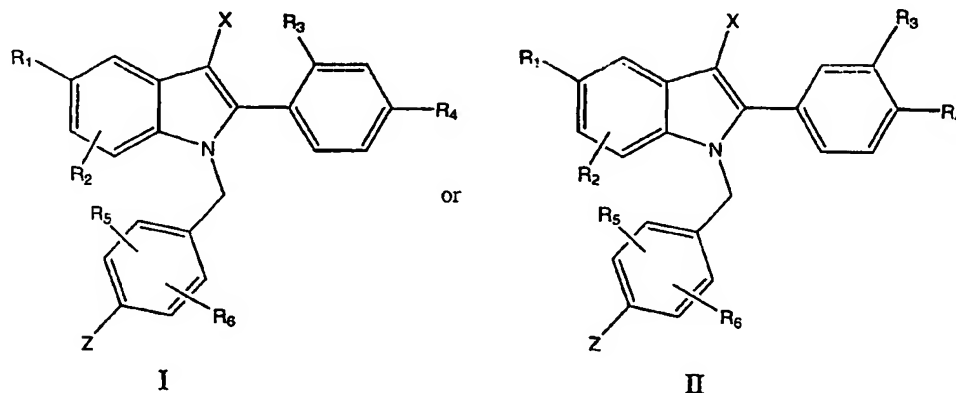
- i) a pharmaceutically effective amount of a bisphosphonate compound, such as, but not limited to, Alendronate, Risedronate, Tiludronate, Ibandronate, Etidronate, Clodronate, Minodronate, Pamidronate, Zoledronate, Incadronate, Olpadronate or Neridronate, or a pharmaceutically acceptable salt of these bisphosphonate compounds;

20

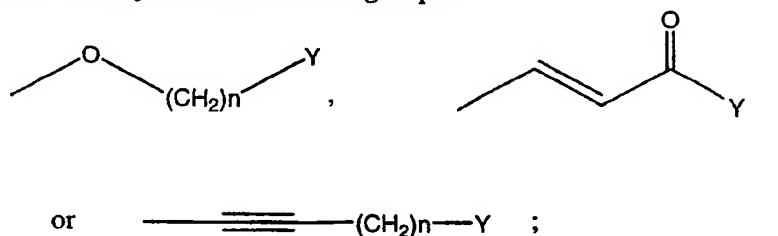
and

- 3 -

ii) a pharmaceutically effective amount of a substituted indole compound of the formulae I or II, below:



5 wherein Z is a moiety selected from the group of:



wherein:

10 R_1 is selected from H, OH or the C_1 - C_{12} esters (straight chain or branched) or C_1 - C_{12} (straight chain or branched or cyclic) alkyl ethers thereof, benzyloxy, or halogens; or C_1 - C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether.

15 R_2 , R_3 , R_5 , and R_6 are independently selected from H, OH or the C_1 - C_{12} esters (straight chain or branched) or C_1 - C_{12} alkyl ethers (straight chain or branched or cyclic) thereof, halogens, or C_1 - C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether, cyano, C_1 - C_6 alkyl (straight chain or branched), or trifluoromethyl, with the proviso that, when R_1 is H, R_2 is not OH;

20 R_4 is selected from H, OH or the C_1 - C_{12} esters (straight chain or branched) or C_1 - C_{12} alkyl ethers (straight chain or branched or cyclic) thereof, benzyloxy, halogens, or C_1 - C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether, cyano, C_1 - C_6 alkyl (straight chain or branched), or trifluoromethyl;

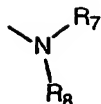
X is selected from H, C_1 - C_6 alkyl, cyano, nitro, trifluoromethyl, halogen;

n is 1, 2 or 3;

- 4 -

Y is selected from:

a) the moiety:



wherein R_7 and R_8 are independently selected from the group of H, $\text{C}_1\text{-C}_6$ alkyl, or phenyl optionally substituted by CN, $\text{C}_1\text{-C}_6$ alkyl (straight chain or branched), $\text{C}_1\text{-C}_6$ alkoxy (straight chain or branched), halogen, -OH, - CF_3 , or - OCF_3 ; or R_7 and R_8 are combined by $-(\text{CH}_2)_p-$, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydroxyl, halo, $\text{C}_1\text{-C}_4$ alkyl, trihalomethyl, $\text{C}_1\text{-C}_4$ alkoxy, trihalomethoxy, $\text{C}_1\text{-C}_4$ alkylthio, $\text{C}_1\text{-C}_4$ alkylsulfinyl, $\text{C}_1\text{-C}_4$ alkylsulfonyl, hydroxy($\text{C}_1\text{-C}_4$)alkyl, - CO_2H , -CN, - $\text{CONH}(\text{C}_1\text{-C}_4)\text{alkyl}$, - NH_2 , $\text{C}_1\text{-C}_4$ alkylamino, di-($\text{C}_1\text{-C}_4$)alkylamino, - $\text{NHSO}_2(\text{C}_1\text{-C}_4)\text{alkyl}$, - $\text{NHCO}(\text{C}_1\text{-C}_4)\text{alkyl}$ and - NO_2 ;

b) a five-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, - $\text{N}(\text{C}_1\text{-C}_4\text{ alkyl})$ -, -N=, and - $\text{S}(\text{O})_m$ -, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, $\text{C}_1\text{-C}_4$ alkyl, trihalomethyl, $\text{C}_1\text{-C}_4$ alkoxy, trihalomethoxy, $\text{C}_1\text{-C}_4$ acyloxy, $\text{C}_1\text{-C}_4$ alkylthio, $\text{C}_1\text{-C}_4$ alkylsulfinyl, $\text{C}_1\text{-C}_4$ alkylsulfonyl, hydroxy($\text{C}_1\text{-C}_4$)alkyl, - CO_2H -, -CN-, - CONHR_1 -, - NH_2 , $\text{C}_1\text{-C}_4$ alkylamino, di($\text{C}_1\text{-C}_4$)alkylamino, - NHSO_2R_1 -, - NHCOR_1 -, - $\text{CONH}(\text{C}_1\text{-C}_4)\text{alkyl}$ -, - $\text{NHSO}_2(\text{C}_1\text{-C}_4)\text{alkyl}$ -, - $\text{NHCO}(\text{C}_1\text{-C}_4)\text{alkyl}$ -, - NO_2 , and phenyl optionally substituted with 1-3 ($\text{C}_1\text{-C}_4$)alkyl;

c) a six-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, - $\text{N}(\text{C}_1\text{-C}_4\text{ alkyl})$ -, -N=, and - $\text{S}(\text{O})_m$ -, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, $\text{C}_1\text{-C}_4$ alkyl, trihalomethyl, $\text{C}_1\text{-C}_4$ alkoxy, trihalomethoxy, $\text{C}_1\text{-C}_4$ acyloxy, $\text{C}_1\text{-C}_4$ alkylthio, $\text{C}_1\text{-C}_4$ alkylsulfinyl, $\text{C}_1\text{-C}_4$ alkylsulfonyl, hydroxy($\text{C}_1\text{-C}_4$)alkyl, - CO_2H -, -CN-, - CONHR_1 -, - NH_2 , $\text{C}_1\text{-C}_4$ alkylamino, di($\text{C}_1\text{-C}_4$)alkylamino, - NHSO_2R_1 -, - NHCOR_1 -, - $\text{CONH}(\text{C}_1\text{-C}_4)\text{alkyl}$ -, - $\text{NHSO}_2(\text{C}_1\text{-C}_4)\text{alkyl}$ -, - $\text{NHCO}(\text{C}_1\text{-C}_4)\text{alkyl}$ -, - NO_2 , and phenyl optionally substituted with 1-3 ($\text{C}_1\text{-C}_4$)alkyl;

- 5 -

d) a seven-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁-C₄alkyl)-, -N=, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-C₄acyloxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, -CN, -CONHR₁, -NH₂, C₁-C₄alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R₁, -NHCOR₁, -CONH(C₁-C₄)alkyl, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, -NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or

e) a bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁-C₄alkyl)-, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-C₄acyloxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H-, -CN, -CONHR₁, -NH₂, C₁-C₄alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R₁, -NHCOR₁, -CONH(C₁-C₄)alkyl, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, -NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄) alkyl;

and the pharmaceutically acceptable salts thereof;

and, optionally

iii) a pharmaceutically effective amount of one or more estrogens, or a pharmaceutically acceptable salt thereof.

The more preferred substituted indole compounds of this invention are those having the general structures I or II, above, wherein:

R₁ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, or halogen;

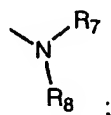
R₂, R₃, R₅, and R₆ are independently selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl, preferably trifluoromethyl, with the proviso that, when R₁ is H, R₂ is not OH;

R₄ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl;

- 6 -

X is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, halogen;

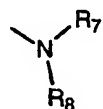
Y is the moiety



R₇ and R₈ are selected independently from H, C₁-C₆ alkyl, or combined by
 5 -(CH₂)_p-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being
 optionally substituted by up to three substituents selected from the group of hydrogen,
 hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄
 alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H,
 -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄alkylamino, di-(C₁-C₄)alkylamino,
 10 -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂;
 and the pharmaceutically acceptable salts thereof.

The rings formed by a concatenated R₇ and R₈, mentioned above, may
 include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine,
 15 hexamethyleneamine or heptamethyleneamine rings.

The most preferred substituted indole compounds of the present invention are
 those having the structural formulas I or II, above, wherein R₁ is OH; R₂ - R₆ are as
 defined above; X is selected from the group of Cl, NO₂, CN, CF₃, or CH₃; and Y is
 20 the moiety



and R₇ and R₈ are concatenated together as -(CH₂)_r-, wherein r is an integer of from 4
 to 6, to form a ring optionally substituted by up to three substituents selected from the
 group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy,
 25 trihalomethoxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy
 (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄alkylamino, di-(C₁-
 C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂;
 and the pharmaceutically acceptable salts thereof.

30 In another embodiment of this invention, when R₇ and R₈ are concatenated
 together as -(CH₂)_p-, wherein p is an integer of from 2 to 6, preferably 4 to 6, the ring
 so formed is optionally substituted with 1-3 substituents selected from a group
 containing C₁-C₃ alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro, -CN.

- 7 -

The invention includes sulfate, sulfamates and sulfate esters of phenolic groups of the substituted indoles. Sulfates can be readily prepared by the reaction of the free phenolic compounds with sulfur trioxide complexed with an amine such as pyridine, trimethylamine, triethylamine, etc. Sulfamates can be prepared by treating the free phenolic compound with the desired amino or alkylamino or dialkylamino sulfamyl chloride in the presence of a suitable base such as pyridine. Sulfate esters can be prepared by reaction of the free phenol with the desired alkanesulfonyl chloride in the presence of a suitable base such as pyridine. Additionally, this invention includes compounds containing phosphates at the phenol as well as dialkyl phosphates. Phosphates can be prepared by reaction of the phenol with the appropriate chlorophosphate. The dialkylphosphates can be hydrolyzed to yield the free phosphates. Phosphinates are also claimed where the phenol is reacted with the desired dialkylphosphinic chloride to yield the desired dialkylphosphinate of the phenol.

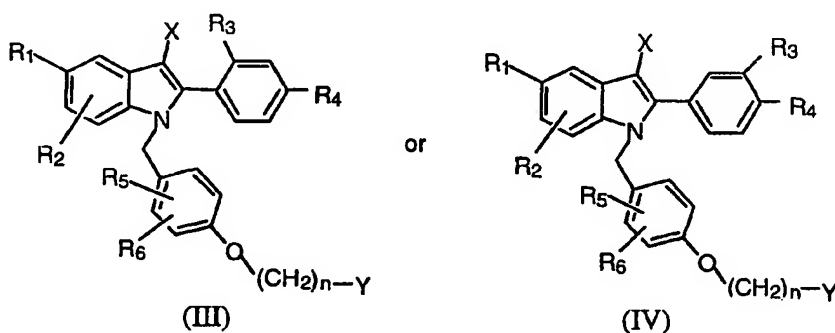
The invention includes acceptable salt forms of the substituted indole formed from the addition reaction with either inorganic or organic acids. Inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, nitric acid useful as well as organic acids such as acetic acid, propionic acid, citric acid, maleic acid, malic acid, tartaric acid, phthalic acid, succinic acid, methanesulfonic acid, toluenesulfonic acid, naphthalenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid are useful. It is known that compounds possessing a basic nitrogen can be complexed with many different acids (both protic and non-protic) and usually it is preferred to administer a compound of this invention in the form of an acid addition salt. Additionally, this invention includes quaternary ammonium salts of the compounds herein. These can be prepared by reacting the nucleophilic amines of the side chain with a suitably reactive alkylating agent such as an alkyl halide or benzyl halide.

The present invention includes methods for strengthening bone and for inhibiting, alleviating, preventing or treating bone disorders including Paget's disease, osteoporosis, including steroid-induced osteoporosis and post-menopausal osteoporosis, tumor-induced hypercalcemia and malignant osteolytic bone disease, bone degradation due to metastases from cancers, such as breast and prostate cancer, and bone destruction characteristic of multiple myeloma, disorders of bone

remodeling, tumor induced hypercalcemia, and malignant osteolytic bone disease. The administration of the regimens of this invention may also be used in methods for reducing the fracture risk and occurrence in a recipient.

5 These methods each comprise administering to a mammal in need thereof a bisphosphonate and a pharmaceutically effective amount of one of the substituted indoles taught herein and optionally a pharmaceutically effective amount of one or more estrogens. These administrations may be therapeutic or prophylactic. Among the preferred substituted indole compounds for use in these methods are 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol, also known as TSE-424, and 2-(4-Hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-1H-indol-5-ol, also known as ERA-923.

The present invention includes methods utilizing, in conjunction with a 15 bisphosphonate compound and, optionally, an estrogen, a first subset or subgroup of substituted indole compounds of the formulas III or IV, below:



20 wherein the variable substituents including R₁, R₂, R₃, R₄, R₅, R₆, n, X, and Y are as defined above, or a pharmaceutically acceptable salt thereof.

The more preferred substituted indole compounds of this first subset of compounds are those having the general structures III or IV, above, wherein:

25 R₁ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, or halogen;

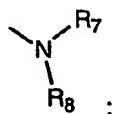
R₂, R₃, R₅, and R₆ are independently selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl, preferably trifluoromethyl, with the proviso that, when R₁ is H, R₂ is not OH;

30 R₄ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl;

- 9 -

X is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, halogen;

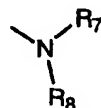
Y is the moiety



R₇ and R₈ are selected independently from H, C₁-C₆ alkyl, or combined by
 5 -(CH₂)_p-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being
 optionally substituted by up to three substituents selected from the group of hydrogen,
 hydroxyl, halo, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-
 C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H,
 -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄alkylamino, diC₁-C₄alkylamino,
 10 -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂;
 and the pharmaceutically acceptable salts thereof.

The rings formed by a concatenated R₇ and R₈, mentioned above, may
 include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine,
 15 hexamethylenamine or heptamethylenamine rings.

The most preferred substituted indole compounds of this first subset of
 compounds are those having the structural formulas I or II, above, wherein R₁ is OH;
 R₂ - R₆ are as defined above; X is selected from the group of Cl, NO₂, CN, CF₃, or
 20 CH₃; and Y is the moiety



and R₇ and R₈ are concatenated together as -(CH₂)_r-, wherein r is an integer of from 4
 to 6, to form a ring optionally substituted by up to three substituents selected from the
 group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy,
 25 trihalomethoxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl,
 hydroxy(C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄alkylamino,
 di(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl and -NO₂;
 and the pharmaceutically acceptable salts thereof.

30 In another embodiment of this first subset of compounds, when R₇ and R₈ are
 concatenated together as -(CH₂)_p-, wherein p is an integer of from 2 to 6, preferably 4
 to 6, the ring so formed is optionally substituted with 1-3 substituents selected from a
 group containing C₁-C₃alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro, -CN.

Among the preferred compounds of this first subset of substituted indoles are the following:

- 5 5-Benzyloxy-2-(4-ethoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-phenyl-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole;
- 10 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(2-diisopropylamino-1-yl-ethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(2-butyl-methylamino-1-ylethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(2-dimethylamino)ethoxy]-benzyl]-1H-indole;
- 15 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-[2-(2-methyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-[2-(3-methyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indole;
- 20 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-[2-((cis)-2,6-Dimethyl-piperidin-1-yl)-ethoxy]-benzyl]-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-[2-(1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-yl)-ethoxy]-benzyl]-1H-indole;
- 25 (1S,4R)-5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-[2-(2-Aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-benzyl]-1H-indole;
- 5-Benzyloxy-2-(4-fluoro-phenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole;
- 30 5-Benzyloxy-2-(4-fluoro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-(4-chloro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;

- 5-Benzyloxy-2-[3,4-methylenedioxy-phenyl]-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-[4-isopropoxy-phenyl]-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;
- 5 5-Benzyloxy-2-[4-methyl-phenyl]-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;
- 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-benzyloxy-2-(3-benzyloxy-phenyl)-3-methyl-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-3-fluoro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;
- 10 5-Benzyloxy-2-(4-benzyloxy-3-fluoro-phenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-(3-methoxy-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-3-methyl-1H-indole;
- 15 5-Benzyloxy-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-(4-trifluoromethoxy-phenyl)-1H-indole;
- (2-{4-[5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-ethyl)-cyclohexyl-amine;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-{4-methylpiperazin-1-yl-ethoxy}-benzyl]-1H-indole;
- 20 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-benzyloxy-2-(3-methoxy-phenyl)-3-methyl-1H-indole;
- 4-{3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole};
- 4-{3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-2-yl}-phenol;
- 25 3-Methyl-2-phenyl-1-[4-(2-piperidine-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 4-{5-Methoxy-3-methyl-1-[4-[2-(piperidin-1-yl)-ethoxy]-benzyl]-1H-indol-2-yl}-phenol;
- 2-(4-methoxy-phenyl)-3-methyl-1-[4-[2-(piperidin-1-yl)-ethoxy]-benzyl]-1H-indol-5-ol;
- 30 5-Methoxy-2-(4-methoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;
- 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-methoxy-2-(4-methoxy-phenyl)-3-methyl-1H-indole;

- 2-(4-Ethoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-ethoxy-phenyl)-3-methyl-1H-indol-5-ol;
- 5 4-{5-Fluoro-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-2-yl}-phenol;
- 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-3-methyl-2-phenyl-1H-indol-5-ol;
- 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-pyrrolidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 10 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 1-[4-(2-Azocan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 15 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-dimethyl-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-diethyl-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 20 1-[4-(2-Dipropylamino-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 1-[4-(2-Dibutylamino-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 1-[4-(2-Diisopropylamino-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 25 1-{4-[2-(Butyl-methyl-amino)-ethoxy]-benzyl}-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 2-(4-Hydroxy-phenyl)-3-methyl-1-{4-[2-(2-methyl-piperidin-1-yl)-ethoxy]-benzyl}-1H-indol-5-ol;
- 30 2-(4-Hydroxy-phenyl)-3-methyl-1-{4-[2-(3-methyl-piperidin-1-yl)-ethoxy]-benzyl}-1H-indol-5-ol;
- 2-(4-Hydroxy-phenyl)-3-methyl-1-{4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-benzyl}-1H-indol-5-ol;

- 1-{4-[2-(3,3-Dimethyl-piperidin-1-yl)-ethoxy]-benzyl}-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 1-{4-[2-((cis)-2,6-Dimethyl-piperidin-1-yl)-ethoxy]-benzyl}-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 5 2-(4-Hydroxy-phenyl)-1-{4-[2-(4-hydroxy-piperidin-1-yl)-ethoxy]-benzyl}-3-methyl-1H-indol-5-ol;
- (1S,4R)-1-{4-[2-(2-Aza-bicyclo [2.2.1] hept-2-yl)-ethoxy]-benzyl}-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 2-(4-Hydroxy-phenyl)-3-methyl-1-{4-[2-(1,3,3-trimethyl-6-azabicyclo[3.2.1]-oct-6-yl)-ethoxy]-benzyl}-1H-indol-5-ol;
- 10 2-(4-Fluoro-phenyl)-3-methyl-1-[4-(2-piperidine-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-fluoro-phenyl)-3-methyl-1H-indol-5-ol;
- 15 2-(3-Methoxy-4-hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 2-Benzo[1,3]dioxol-5-yl-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 2-(4-Isopropoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 20 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-isopropoxy-phenyl)-3-methyl-1H-indol-5-ol;
- 2-(4-Cyclopentyloxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 25 3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-(4-trifluoromethylphenyl)-1H-indol-5-ol;
- 3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-p-tolyl-1H-indol-5-ol;
- 2-(4-Chloro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 30 2-(2,4-Dimethoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 2-(3-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;

- 14 -

- 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(3-hydroxy-phenyl)-3-methyl-1H-indole-5-ol;
- 2-(3-Fluoro-4-hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 5 2-(3-Fluoro-4-hydroxy-phenyl)-3-methyl-1-[4-(azepan-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 2-(3-Methoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole-5-ol;
- 3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-(4-trifluoromethoxy-phenyl)-1H-indole-5-ol;
- 10 3-Chloro-2-(4-hydroxy-phenyl)-1-[4-(2-pyrrolidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 3-Chloro-2-(4-hydroxy-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 15 3-Chloro-2-(4-hydroxy-phenyl)-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 3-Chloro-2-(4-hydroxy-2-methyl-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 2-(4-Hydroxy-phenyl)-3-ethyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 20 5-Hydroxy-2-(4-Hydroxy-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole-3-carbonitrile;
- 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-hydroxy-2-(4-hydroxy-phenyl)-1H-indole-3-carbonitrile;
- 25 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-chloro-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-chloro-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-(2-methyl-4-benzyloxy-phenyl)-3-chloro-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;
- 30 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-ethyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;

- 15 -

5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-cyano-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;

5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-cyano-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole;

5 Di-propionate of 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;

Di-pivalate of 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;

10 5-Benzyloxy-2-(4-benzyloxy-phenyl)-1-[4-(3-piperidin-1-yl-propoxy)benzyl]-3-methyl-1H-indole;

2-(4-Hydroxy-phenyl)-3-methyl-1-[4-[3-(piperidin-1-yl)-propoxy]-benzyl]-1H-indol-5-ol;

2-(4-Hydroxy-phenyl)-1-[3-methoxy-4-(2-piperidin-1-yl-ethoxy)-benzyl]-3-methyl-1H-indol-5-ol;

15 2-(4-Hydroxy-phenyl)-1-[3-methoxy-4-(2-azepan-1-yl-ethoxy)-benzyl]-3-methyl-1H-indol-5-ol;

5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[3-Methoxy-4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;

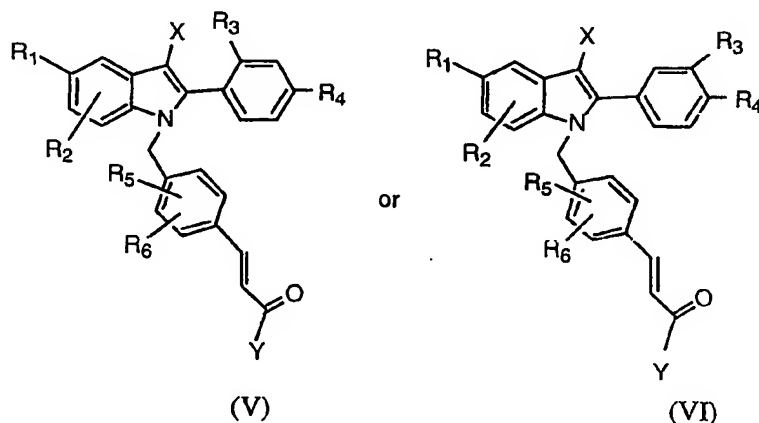
20 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[2-Methoxy-4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole;

2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;

or the pharmaceutically acceptable salts thereof.

25 The compounds of this first subset or subgroup of compounds can be produced by the methods described in EP 0 802 183 A1, published October 22, 1997, and U.S. Patent No. 5,780,497, the subject matter of which is incorporated herein by reference, or by other methods known in the art. Aryloxy-alkyl-dialkylamines or
aryloxy-alkyl-cyclic amines useful as intermediates in the production of the
30 compounds above can be produced and used as disclosed in WO 99/19293, published April 22, 1999, the subject matter of which is also incorporated herein by reference.

A second subset or subgroup of substituted indole compounds useful with this invention includes those of formulas (V) or (VI), below:



wherein the variable substituents including R₁, R₂, R₃, R₄, R₅, R₆, n, X, and Y are as defined above, or a pharmaceutically acceptable salt thereof.

Among the preferred substituted indole compounds of this second subset or subgroup are the following:

(E)-N,N-Diethyl-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;

1(E)-N-tert-butyl-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;

(E)-Pyrollidino-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;

(E)-N,N-Dimethyl-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;

(E)-N,N-Dibutyl-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;

(E)-N-Butyl,N'-methyl-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;

(E)-Morpholinino-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;

(E)-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;

(E)-N-Methyl-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;

- 17 -

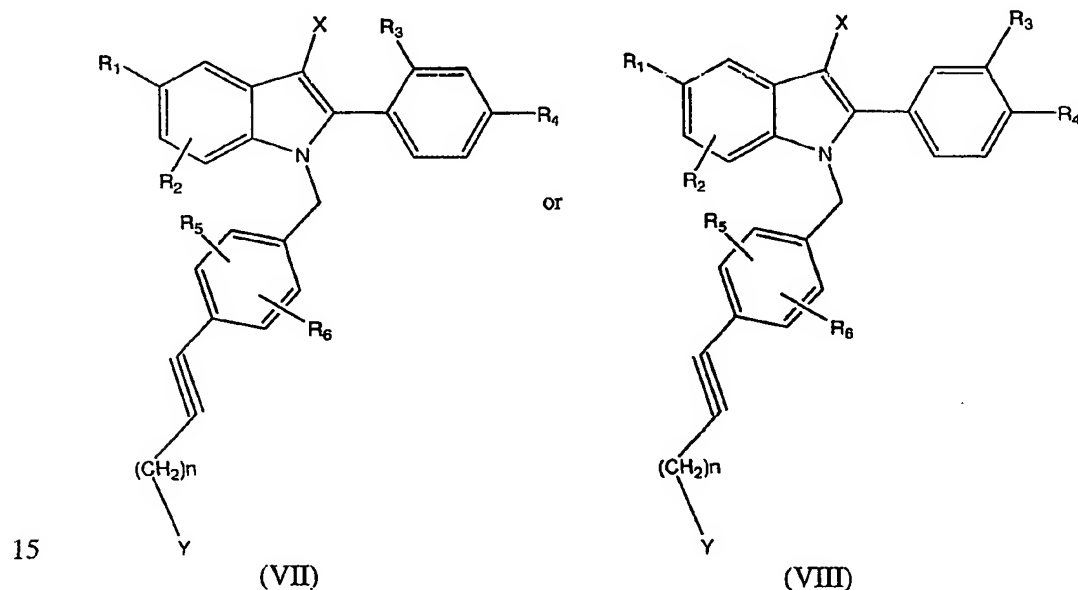
(E)-N,N-Dibutyl-3-{4-[5-hydroxy-2-(4-fluoro-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;

(E)-N-Butyl,N'-Methyl-3-{4-[5-hydroxy-2-(4-fluoro-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;

5 as well as the pharmaceutically acceptable salts and esters thereof.

The compounds of this second subset or subgroup of substituted indole compounds can be produced by the methods described in EP 0 802 184 A1, published October 22, 1997, which is incorporated herein by reference, or by other methods
10 known in the art.

A third subset of substituted indole compounds useful with the present invention include those of the formulae VII and VIII:



wherein n is 1, 2 or 3 and the variable substituents including R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , n , X , and Y are as defined above, or a pharmaceutically acceptable salt thereof.

20 Among the preferred compounds of this third subset of substituted indoles are:
2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(3-N,N-dimethyl-1-yl-prop-1-ynyl)-benzyl]-1H-indol-5-ol;
2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(3-piperidin-1-yl-prop-1-ynyl)-benzyl]-1H-indol-5-ol; and

- 18 -

2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(3-pyrrolidin-1-yl-prop-1-ynyl)-benzyl]-1H-indol-5-ol;

or pharmaceutically acceptable salts or esters thereof.

5 The compounds of this third subset or subgroup of substituted indole compounds can be produced by the methods described in U.S. Patent No. 5,880,137 (Miller et al.), which is incorporated herein by reference, or by other methods known in the art.

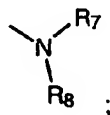
10 Within each of the first, second and third subsets of substituted indole compounds of this invention are further subdivisions of more preferred substituted indole compounds having the general structures I through VIII, above, wherein:

R_1 is selected from H, OH or the C_1 - C_{12} esters or alkyl ethers thereof, halogen;

15 R_2 , R_3 , R_4 , R_5 , and R_6 are independently selected from H, OH or the C_1 - C_{12} esters or alkyl ethers thereof, halogen, cyano, C_1 - C_6 alkyl, or trihalomethyl, preferably trifluoromethyl, with the proviso that, when R_1 is H, R_2 is not OH;

X is selected from H, C_1 - C_6 alkyl, cyano, nitro, trifluoromethyl, halogen;

Y is the moiety



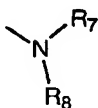
20 R_7 and R_8 are selected independently from H, C_1 - C_6 alkyl, or combined by $-(CH_2)_p-$, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C_1 - C_4 alkyl, trihalomethyl, C_1 - C_4 alkoxy, trihalomethoxy, C_1 - C_4 alkylthio, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonyl, hydroxy (C_1 - C_4)alkyl, $-CO_2H$,
 25 $-CN$, $-CONH(C_1-C_4)alkyl$, $-NH_2$, C_1 - C_4 alkylamino, $diC_1-C_4alkylamino$, $-NHSO_2(C_1-C_4)alkyl$, $-NHCO(C_1-C_4)alkyl$, and $-NO_2$;
 and the pharmaceutically acceptable salts thereof.

30 The rings formed by a concatenated R_7 and R_8 , mentioned above, may include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine, hexamethyleneamine or heptamethyleneamine rings.

35 The most preferred substituted indole compounds of the present invention are those having the structural formulas I through VIII, above, wherein R_1 is OH; R_2 - R_6

- 19 -

are as defined above; X is selected from the group of Cl, NO₂, CN, CF₃, or CH₃; and Y is the moiety



and R₇ and R₈ are concatenated together as -(CH₂)_r-, wherein r is an integer of from 4 to 6, to form a ring optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂;
 10 and the pharmaceutically acceptable salts thereof.

In another embodiment of the substituted indoles of this invention, when R₇ and R₈ are concatenated together as -(CH₂)_p-, wherein p is an integer of from 2 to 6, preferably 4 to 6, the ring so formed is optionally substituted with 1-3 substituents
 15 selected from a group containing C₁-C₃ alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro, -CN.

The invention includes sulfate, sulfamates and sulfate esters of phenolic groups. Sulfates can be readily prepared by the reaction of the free phenolic
 20 compounds with sulfur trioxide complexed with an amine such as pyridine, trimethylamine, triethylamine, etc. Sulfamates can be prepared by treating the free phenolic compound with the desired amino or alkylamino or dialkylamino sulfamyl chloride in the presence of a suitable base such as pyridine. Sulfate esters can be prepared by reaction of the free phenol with the desired alkanesulfonyl chloride in the
 25 presence of a suitable base such as pyridine. Additionally, this invention includes compounds containing phosphates at the phenol as well as dialkyl phosphates. Phosphates can be prepared by reaction of the phenol with the appropriate chlorophosphate. The dialkylphosphates can be hydrolyzed to yield the free phosphates. Phosphinates are also claimed where the phenol is reacted with the
 30 desired dialkylphosphinic chloride to yield the desired dialkylphosphinate of the phenol.

The invention includes acceptable salt forms formed from the addition reaction with either inorganic or organic acids. Inorganic acids such as hydrochloric

acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, nitric acid useful as well as organic acids such as acetic acid, propionic acid, citric acid, maleic acid, malic acid, tartaric acid, phthalic acid, succinic acid, methanesulfonic acid, toluenesulfonic acid, naphthalenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid are useful. It is known that compounds possessing a basic nitrogen can be complexed with many different acids (both protic and non-protic) and usually it is preferred to administer a compound of this invention in the form of an acid addition salt. Additionally, this invention includes quaternary ammonium salts of the compounds herein. These can be prepared by reacting the nucleophilic amines of the side chain with a suitably reactive alkylating agent such as an alkyl halide or benzyl halide.

When an estrogen is used estrogens useful in the formulations of this invention include estrone, estriol, equilin, estradiene, equilenin, ethinyl estradiol, 17 β -estradiol, 17 α -dihydroequilenin, 17 β -dihydroequilenin (U.S. Patent 2,834,712), 17 α -dihydroequilin, 17 β -dihydroequilin, menstranol and conjugated estrogenic hormones, such as those in Wyeth-Ayerst Laboratories' Premarin[®] products (P.O. Box 8299, Philadelphia, PA 19101, U.S.A.). Phytoestrogens, such as equol or enterolactone, may also be used in the present formulations and methods. A preferred embodiment of this invention comprises pharmaceutical compositions and methods of treatment utilizing conjugated estrogenic hormones, such as those in Wyeth-Ayerst Laboratories' Premarin[®] products, with one or more compounds of Formulas (I) or (III) listed herein. Esterified estrogens, such as those sold by Solvay Pharmaceuticals, Inc. under the Estratab[®] tradename, may also be used with the present formulations. Also preferred for use with the present invention are the salts of the applicable estrogens, most preferably the sodium salts. Examples of these preferred salts are Sodium estrone sulfate, Sodium equilin sulfate, Sodium 17 α -dihydroequilin sulfate, Sodium 17 α -estradiol sulfate, Sodium Delta8,9- dehydroestrone sulfate, Sodium equilenin sulfate, Sodium 17 β -dihydroequilin sulfate, Sodium 17 α -dihydroequilenin sulfate, Sodium 17 β -estradiol sulfate, Sodium 17 β -dihydroequilenin sulfate, Estrone 3-sodium sulfate, Equilin 3-sodium sulfate, 17 α -Dihydroequilin 3-sodium sulfate, 3 β -Hydroxy-estra-5(10),7-dien-17-one 3-sodium sulfate, 5 α -Pregnan-3 β -20R-diol 20-sodium sulfate, 5 α -Pregnan-3 β ,16 α -diol-20-one 3-sodium sulfate, delta(8,9)-Dehydroestrone 3-sodium sulfate, Estra-3 β , 17 α -diol 3-sodium sulfate, 3 β -Hydroxy-estr-5(10)-en-17-one 3-sodium sulfate or 5 α -Pregnan-3 β ,16 α ,20R-triol 3-sodium sulfate. Preferred salts of estrone include, but are not limited to, the sodium and piperate salts.

- 21 -

Among the most preferred estrogens for use with this invention are the conjugated estrogens of the Premarin® brand products.

Among the most preferred embodiments of this invention are methods
5 combining the administration in a mammal of pharmaceutically effective amounts of:

a) a substituted indole compound selected from 1-[4-(2-Azepan-1yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol, also known as TSE-424, and 2-(4-Hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol, also known as ERA-923, or a pharmaceutically acceptable salt of TSE-424
10 or ERA-923; and

b) a bisphosphonate compound selected from the group of , Alendronate, Risedronate, Tiludronate, Ibandronate, Etidronate, Clodronate, Minodronate, Pamidronate, Zoledronate, Incadronate, Olpadronate or Neridronate, or a pharmaceutically effective salt of one of these bisphosphonate compounds, and
15 optionally

c) the conjugated estrogenic hormones, such as those of the Premarin® brand products marketed by Wyeth-Ayerst Laboratories.

It is understood that the dosage, regimen and mode of administration of these
20 compounds will vary according to the extent of the malady and the individual being treated and will be subject to the judgement of the medical practitioner involved. It is preferred that the administration of one or more of the bisphosphonates and substituted indole compounds herein begin at a low dose and be increased until the desired effects are achieved.

25

Effective administration of these compounds may be given at an effective dose of from about 0.1 mg/day to about 500 mg/day. Preferably, administration will be from about 1 mg/day to about 200 mg/day in a single dose or in two or more divided doses. Such doses may be administered in any manner useful in directing the
30 active compounds herein to the recipient's bloodstream, including orally, parenterally (including intravenous, intraperitoneal and subcutaneous injections), and transdermally. For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such
35 administrations may be carried out using the present compounds, or pharmaceutically

acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

When the active ingredient in the formulations and methods of this invention is 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol, also known as TSE-424, or a pharmaceutically acceptable salt thereof, the preferred daily dosage for oral delivery is from about 0.1 to about 50 mg, preferably from about 2.5 to about 40 mg per day.

When the active ingredient in the formulations and methods of this invention is 2-(4-Hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-1H-indol-5-ol, also known as ERA-923, or a pharmaceutically acceptable salt form thereof, the preferred daily dosage for oral delivery is from about 0.1 to about 200 mg, preferably from about 2.5 to about 100 mg per day.

Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, , xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

The pharmaceutically effective doses for the bisphosphonates and substituted indoles and the estrogens when used herein will be understood to be those sufficient to provide a desirable diminution in the risk or prevalence of the bone disease or disorder in question. Preferably the compounds will be administered at a dose effective to maintain or increase bone mass density in the recipient, as directed by a medical professional.

The bisphosphonate compounds of these methods may be administered in regimens and at dosages known in the art. For instance, alendronate sodium, which is sold by Merck & Co., Inc. under the Fosamax[®] name, has a recommended dosage of 10 mg per day for treatment of osteoporosis in postmenopausal women and 5 mg per day for the prevention of osteoporosis in postmenopausal women. Tiludronate sodium, marketed by Sanofi Pharmaceuticals under the Skelid[®] brandname, may be taken as a single 400 mg daily oral dose. Etidronate sodium, offered by MGI Pharma, Inc. under the Didronel[®] name, has a recommended daily intravenous infusion dose of 7.5 mg/kg body weight/day for three successive days. Risedronate (Actonel[™]; jointly marketed by Procter and Gamble Pharmaceuticals and Hoechst Marion Roussel) has been approved by the FDA for use in Paget's disease of the bone (30-mg tablets) Risedronate was shown to be effective in clinical trials.

The estrogens herein may be administered according to the regimens and doses known in the art. For instance, the preferred Premarin[®] conjugated estrogen tablets may be administered as described in pages 3302-3305 of the Physicians' Desk Reference, 54 Edition, 2000, Medical Economics Company, Inc., Montvale, NJ 07645-1742. Other commercially available estrogens useful with the present invention include OGEN[®] (estropipate tablets), ESTRATAB[®] (esterified estrogens tablets), ESTRACE[®] estradiol vaginal cream, CLIMARA[®] (estradiol transdermal system), ESTRADERM[®] (transdermal system), MENEST[™] (esterified estrogens tablets), ORTHO-EST[®] (estropipate tablets), CENESTIN[™] (synthetic conjugated estrogens), ALORA[®] (estradiol transdermal system), ESTINYL[®] (ethynil estradiol), and the VIVELLE[®] and VIVELLE-DOT[®] (estradiol transdermal systems). Each of these commercially available estrogen products can be administered as described in their relevant portions of the Physicians' Desk Reference, 54 Edition, 2000.

- 24 -

The following table lists estrogen replacement therapeutics and dosage strengths available in the United States and/or Europe

Generic Name	Brand Name	Strength
Oral estrogens		
Conjugated equine estrogens (natural)	Premarin	0.3, 0.625, 0.9, 1.25, 2.5 mg
Conjugated estrogens (synthetic)	Cenestin	0.625, 0.9 mg
Esterified estrogens (75-80% estrone sulfate 6-15% equilin sulfate derived from plant sterols)	Estratab	0.3, 0.625, 1.25, 2.5 mg
Estropipate (Piperazine estrone sulfate)	Ogen Ortho-Est	0.625, 1.25, 2.5 mg
Micronized estradiol	Estrace	0.5, 1.0, 2.0 mg
Raloxifene (selective estrogen receptor modulator)	Evista	60 mg
Esterified estrogens and methylestosterone	Estratest	1.25 mg esterified estrogen and 2.5 mg methylestosterone
	Estratest HS	0.625 mg esterified estrogen and 1.25 mg methylestosterone
Estradiol valerate	Climaval	1 mg, 2 mg
Estradiol	Elleste Solo	1 mg, 2 mg
Estradiol	Estrofem	2 mg
Estradiol	Estrofem Forte	4 mg
Piperazine esterone sulfate	Harmogen	1.5 mg
Combination: Estrone	Hormonin	1.4 mg
Estradiol		0.6 mg
Estradiol		0.27 mg
Estradiol valerate	Progynova	1 mg, 2 mg
Estradiol	Zumenon	1 mg, 2 mg
Transdermal estrogens		
Estradiol	Alora (twice weekly)	0.025, 0.0375, 0.05, 0.075,
	Climara (weekly)	0.1 mg of estradiol released
	Estraderm (2x weekly)	daily (dose options for
	Fem Patch (weekly)	various
	Vivelle (twice weekly)	products)
Estradiol	Dermestril	
Estradiol	Estraderm	25, 50, 100 µg
Estradiol	Evorel (System)	25, 50, 100 µg
Estradiol	Fematrix	25, 50, 75, 100 µg
Estradiol	Menorest	40, 80 µg
	Progynova TS	25, 37.5, 50, 75 µg
Estradiol	And TS Forte (Climara)	50, 100 µg
Vaginal estrogens		
Conjugated equine estrogens	Premarin vaginal cream	
Dienestrol	Ortho dienestrol cream	0.625 mg/g
Estradiol	Estring	0.1 mg/g
Estropipate	Ogen vaginal cream	7.5 µg
Micronized estradiol	Estrace vaginal cream	1.5 mg/g
		1.0 mg/g

- 25 -

The joint administration of two groups of compounds in these methods will be determined by a medical professional based upon the condition of the recipient and the malady for which the prophylaxis or treatment is provided. Administration of the two compounds may begin simultaneously or one may be introduced into an ongoing regimen of the other. For shorter term bisphosphonate administrations, such as the infusion of etidronate sodium, an initial regimen of the substituted indole compound may be preferred, which may continue through the term of bisphosphonate administration and beyond.

The joint administration of the three groups of compounds in the methods of this invention will likewise be determined by a medical professional based upon the condition of the recipient and the malady for which the prophylaxis or treatment is provided. For prophylaxis, such as the combination of one of the substituted indoles herein and alendronate and one or more estrogens, for prevention of osteoporosis, administration of all compounds of the regimen may begin simultaneously or one may be introduced into an ongoing regimen of the other. For shorter term bisphosphonate administrations, such as the infusion of etidronate sodium, an initial regimen of the substituted indole compound and one or more estrogens may be preferred, which may continue through the term of bisphosphonate administration and beyond.

Preferably, the pharmaceutical compositions of the methods herein are supplied in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

The substituted indole compound(s) and bisphosphonate(s), and estrogens when utilised, of the present formulations may be administered in separate dosage units, such as separate pills, tablets, powders, etc., or combined into one formulation. When optimum dosages for the indole compounds and the bisphosphonates of these formulations have been determined, it may preferable to incorporate both into a single formulation for ease of administration. It is also understood that the formulations herein may or may not include other pharmaceutically active components.

- 26 -

This invention also includes kits or packages of pharmaceutical formulations designed for use in the regimens and methods described herein. These kits are preferably designed for daily oral administration over the specified term or cycle of administration, preferably for the number of prescribed oral administrations per day, and organized so as to indicate a single oral formulation or combination of oral formulations to be taken on each day of the regimen or cycle. Preferably each kit will include oral tablets to be taken on each the days specified, in some embodiments one oral tablet will contain each of the combined daily dosages indicated and in other
5
10
15
20
25
30
embodiments the administrations of the separate compounds will be present in separate formulations or compositions. It is most preferable that the package or kit shall have a calendar or days-of-the-week designation directing the administration of the appropriate compositions on the appropriate day or time.

In a preferred embodiment, a package or kit of this invention will include individual oral dosage formulations for each of the components of the invention. For instance one daily dosage tablet of a bisphosphonate selected Alendronate, Risedronate, Tiludronate, Ibandronate, Etidronate, Clodronate, Minodronate, Pamidronate, Zoledronate, Incadronate, Olpadronate or Neridronate, or a
15
20
25
30
pharmaceutically acceptable salt thereof, and one orally administerable formulation for a substituted indole compound of this invention, preferably 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or 2-(4-Hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-1H-indol-5-ol or a pharmaceutically acceptable salt thereof, and optionally one daily dosage Premarin® conjugated estrogen tablet, for each day of a specified regimen. It will be understood that any or each of these components may be divided in the kit or package into multiple doses to be administered over the course of each day. In another preferred embodiment, the kit or package comprises a one month supply of the components described herein, i.e. from 28 to 31 daily administration amounts of each component.

30
Solid oral formulations, preferably in the form of a film coated tablet or capsule, useful for this invention include the active pharmacological agents disclosed herein in combination with carrier or excipient systems having the components:

a) a filler and disintegrant component comprising from about 5% to about
35 82% by weight (wght) of the total formulation, preferably between about 30% and

- 27 -

about 80% of the formulation, of which from about 4% to about 40% by weight of the total formulation comprises one or more pharmaceutically acceptable disintegrants;

b) optionally, a wetting agent comprising from about 0.2 to about 5% of the composition (wght), such as selected from the group of sodium lauryl sulfate, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl ethers, sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene castor oil derivatives, docusate sodium, quaternary ammonium compounds, sugar esters of fatty acids and glycerides of fatty acids;

c) a lubricant comprising from about 0.2% to about 10% of the composition (wght), such as selected from the group of magnesium stearate or other metallic stearates (e.g. calcium stearate or zinc stearate), fatty acid esters (e.g. sodium stearyl fumarate), fatty acids (e.g. stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oils, leucine, polyethylene glycols, metallic lauryl sulfates and sodium chloride; and

d) optionally, a glidant comprising from about 0.1% to about 10% (wght) of the composition, the glidant selected from those known in the art, including from the group of silicon dioxide, talc, metallic stearates, calcium silicate, or metallic lauryl sulfates.

While the formulations described herein may be used in an uncoated or non-encapsulated solid form, preferably the final compositions are coated or encapsulated. The pharmacological compositions may be optionally coated with a film coating, preferably comprising from about 0.3% to about 8% by weight of the overall composition. Film coatings useful with the present formulations are known in the art and generally consist of a polymer (usually a cellulosic type of polymer), a colorant and a plasticizer. Additional ingredients such as wetting agents, sugars, flavors, oils and lubricants may be included in film coating formulations to impart certain characteristics to the film coat. The compositions and formulations herein may also be combined and processed as a solid, then placed in a capsule form, such as a gelatin capsule.

The filler component listed above may utilize the filler or binder components known in the art for solid oral formulations. Pharmaceutically acceptable fillers or

- 28 -

binding agents selected from those known in the art including, but not limited to, lactose, microcrystalline cellulose, sucrose, mannitol, calcium phosphate, calcium carbonate, powdered cellulose, maltodextrin, sorbitol, starch, or xylitol.

5 In conjunction with or in place of the materials listed above for the filler component, the present formulations utilize disintegrant agents. These disintegrants may be selected from those known in the art, including pregelatinized starch and sodium starch glycolate. Other useful disintegrants include croscarmellose sodium, 10 crospovidone, starch, alginic acid, sodium alginate, clays (e.g. veegum or xanthan gum), cellulose floc, ion exchange resins, or effervescent systems, such as those utilizing food acids (such as citric acid, tartaric acid, malic acid, fumaric acid, lactic acid, adipic acid, ascorbic acid, aspartic acid, erythorbic acid, glutamic acid, and succinic acid) and an alkaline carbonate component (such as sodium bicarbonate, calcium carbonate, magnesium carbonate, potassium carbonate, ammonium 15 carbonate, etc.). The disintegrant(s) useful herein will comprise from about 4% to about 40% of the composition by weight, preferably from about 15% to about 35%, more preferably from about 20% to about 35%. Some components may have multiple functions in the formulations of this invention, acting e.g. as both a filler and a disintegrant, such a component may be referred to as a filler disintegrant and its 20 function in a specific formulation may be singular even though its properties may allow multiple functionality.

 The pharmaceutical formulations and carrier or excipient systems herein preferably also contain an antioxidant or a mixture of antioxidants, most preferably 25 ascorbic acid. Other antioxidants which may be used include sodium ascorbate and ascorbyl palmitate, preferably in conjunction with an amount of ascorbic acid. A preferable range for the antioxidant(s) is from about 0.5% to about 15% by weight, most preferably from about 0.5% to about 5% by weight.

30 Among the formulations of this invention are pharmaceutical formulations containing a pharmaceutically effective amount of an active pharmacological agent and a carrier or excipient system comprising:

- 29 -

a) a filler and disintegrant component comprising between about 50% and about 87% of the formulation, with from about 4% to about 40% of the formulation comprising one or more disintegrant agents;

5 b) a wetting agent comprising between about 0.5% and about 2.7% of the formulation;

c) a lubricant comprising between about 0.2% and about 5.5% of the formulation; and

d) a glidant comprising between about 0.1% and about 5.5% of the formulation.

10

The percentages listed in the formulations above indicate percentages by weight of the total weight of the components listed from a) to d). The formulations above also preferably contain an optional antioxidant component, preferably ascorbic acid, at a concentration of from about 0.5% to about 5.5% by weight of the formulation. The formulations are also preferably contained within a pharmaceutically acceptable capsule, such as a gel capsule, or coated with a film coating comprising from about 0.3% to about 8% by weight of the formulation.

20 This invention also comprises a pharmaceutical carrier or excipient systems useful in pharmaceutical compositions utilizing as an active ingredient one or more of the compounds described herein, or a pharmaceutically acceptable salt thereof, as described herein. These pharmaceutical carrier or excipient systems comprise, by weight:

25 a) a filler and disintegrant component comprising between about 54% and about 80% of the formulation, with the disintegrant agent(s) therein comprising from about 4% to about 40% by weight of the overall formulation;

b) a wetting agent comprising between about 0.55% and about 2.5% of the formulation;

30 c) a lubricant comprising between about 0.2% and about 5.5% of the formulation; and

d) a glidant comprising between about 0.1% and about 5.0% of the formulation.

- 30 -

The more preferred carrier or excipient systems above also optionally and preferably contain an antioxidant component, preferably ascorbic acid, at a concentration of from about 0.1% to about 5.0% by weight.

- 5 Among the carrier or excipient systems of this invention are those comprising:
- a) a filler and disintegrant component, as described above, comprising between about 50% and about 87% of the formulation, the disintegrant(s) therein comprising from about 25% to about 35% of the formulation, by weight;
 - b) a wetting agent comprising between about 0.55% and about 2.7% of
10 the formulation;
 - c) a lubricant comprising between about 0.2% and about 5.5% of the formulation;
 - d) a glidant comprising between about 0.1% and about 5.5% of the formulation; and
 - 15 e) an antioxidant component, preferably ascorbic acid, at a concentration of from about 0.1% to about 5.5% by weight.

Accordingly this invention further provides a product comprising a compound of formula I or II as defined above or a pharmaceutically acceptable salt thereof and a
20 bisphosphonate or a pharmaceutically acceptable salt thereof, and optionally one or more estrogens, or a pharmaceutically acceptable salt thereof for administration as a combined preparation for simultaneous, separate or sequential use in treatment of bone disorders in a mammal.

25 This invention further provides a pharmaceutical composition comprising a compound of formula I or II as defined above or a pharmaceutically acceptable salt thereof, and a bisphosphonate or a pharmaceutically acceptable salt thereof and optionally one or more estrogens, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

30

Example 1. TSE-424 Acetate –Rapid Dissolution Formulations

Ingredient	without Ascorbic Acid	with Ascorbic Acid
TSE-424 acetate, micronized*	10.00	10.00
Lactose NF fast flow	33.10	31.60
Microcrystalline Cellulose, NF (Avicel PH101)	25.00	25.00
Starch 1500	20.00	20.00
Sodium Lauryl Sulfate NF	1.50	1.50
Sodium Starch Glycolate	10.00	10.00
Ascorbic Acid USP	--	1.5
Syloid 244 FP	0.15	0.15
Magnesium Stearate	0.25	0.25

* Amount in formula is adjusted for actual potency of TSE-424 as free base.

5 Corresponding adjustment made with Lactose.

The formulations given above in Table 1 were prepared by incorporating a portion of the excipients in the granulation and a portion is also added in the final blending steps as dry powders. A dissolution profile generated for the formulations demonstrated almost 90% release of the drug in 30 minutes. Thus, the unique combination of disintegrants and soluble diluents plus the incorporation of both granulated and powdered solids into the composition ensures the fastest release of drug.

15 Wet granulation of the formulations as described in Table 1 may be carried out by mixing the drug and ascorbic acid with a portion of the lactose, microcrystalline cellulose, pregelatinized starch and sodium starch glycolate. The sodium lauryl sulfate is dissolved in the water and used to granulate the mixture of powders in a high shear mixer. The granulation is dried in a fluid bed dryer to a moisture of 2-3%. The particle size of the dried granulation is controlled by passing through a mill equipped with knife-edged blades and using a 20- or 30-mesh screen. The silicon dioxide and remaining lactose, microcrystalline cellulose, pregelatinized

- 32 -

starch, and sodium starch glycolate are mixed with the milled granulation in a tumble-type mixer. The final blend is prepared by adding magnesium stearate to the tumble-type mixer and mixing. Compression is carried out on a rotary tablet press using appropriate size tooling. Coating is performed in conventional coating pans and
 5 applying the coating suspension to achieve a suitable film coat.

Example 2. Modified TSE-424 formulation

%w/w

Ingredient	5% granulation
TSE-424 acetate, micronized ^a	5.00
Lactose NF	41.00
Microcrystalline Cellulose, NF	35.00
Pregelatinized Starch NF	10.00
Sodium Lauryl Sulfate NF	1.50
l-Ascorbic Acid USP	1.50
Sodium Starch Glycolate NF	5.50
Magnesium Stearate NF	0.50
Pur. Water USP ^b	qs

- 10 ^a Amount in formula is adjusted for actual potency of TSE-424 as free base.
 Corresponding adjustment made with Lactose.
- ^b Used in process but does not appear in the final product.

Example 3. ERA-923 formulations

%w/w

Ingredient	10.86% granulation	11.19% granulation	17.5% granulation	17.9% granulation
ERA-923, micronized ^a	10.867	11.193	17.489	17.909
Lactose NF	29.000	29.000	17.380	18.000
Microcrystalline Cellulose, NF	40.633	42.807	38.000	39.090
Pregelatinized Starch NF	10.000	10.000	14.630	15.000
Sodium Lauryl Sulfate NF	2.500	—	2.500	--
l-Ascorbic Acid USP	1.500	1.500	1.500	1.500
Sodium Starch Glycolate NF	5.000	5.000	8.000	8.000
Magnesium Stearate NF	0.500	0.500	0.500	0.500
Pur. Water USP ^b	qs	qs	qs	qs

5 ^a As the Hydrochloride Monohydrate. Quantity is adjusted based on the actual potency (theory = 89.34%).

^b Used in process but does not appear in the final product.

ERA-923 tablets are compressed to a tablet weight of up to 640 mg to achieve the target dose (up to 100 mg). Tablets may then be film coated.

10

Example 4. TSE-424 at 5 % Granulation

15 A preferred carrier or excipient system for formulating a granulation of from about 2 to about 8% by weight of one of the active pharmacological agents of this invention, preferably about 5%, may be produced utilizing the carrier or excipient components on a weight percentage; lactose from about 32% to about 38%, microcrystalline cellulose from about 32% to about 38%, pregelatinized starch from about 12% to about 16%, ascorbic acid from about 1% to about 2%, sodium lauryl sulfate from about 1% to about 2%, sodium starch glycolate from about 4% to about 8%, silicon dioxide from about 0.1% to about 0.2% and magnesium stearate from
20 about 0.3% to about 0.7%.

- 34 -

A formulation of this invention utilizing TSE-424 as the active ingredient at a 5% granulation was prepared utilizing the components listed below in a granulation part of components and a dry part.

5			
	Item No.	Ingredients	Mg/Unit
	Granulation Part:		
	1	TSE-424 acetate	5.00
10	2	Lactose NF	26.60
	3	Microcrystalline Cellulose NF	25.00
	4	Pregelatinized Starch NF	10.00
	5	Ascorbic Acid USP	1.50
	6	Sodium Lauryl Sulfate NF	1.50
15	7	Sodium Starch Glycolate NF	4.00
	8	Water, Purified USP	Q.S.

			73.60
	Dry Part:		
20	9	Lactose NF (fast flo)	9.75
	10	Microcrystalline Cellulose NF	10.00
	11	Pregelatinized Starch NF	4.00
	12	Sodium Starch Glycolate NF	2.00
	13	Silicon Dioxide NF	0.15
25	14	Magnesium Stearate NF	0.50

			100.00

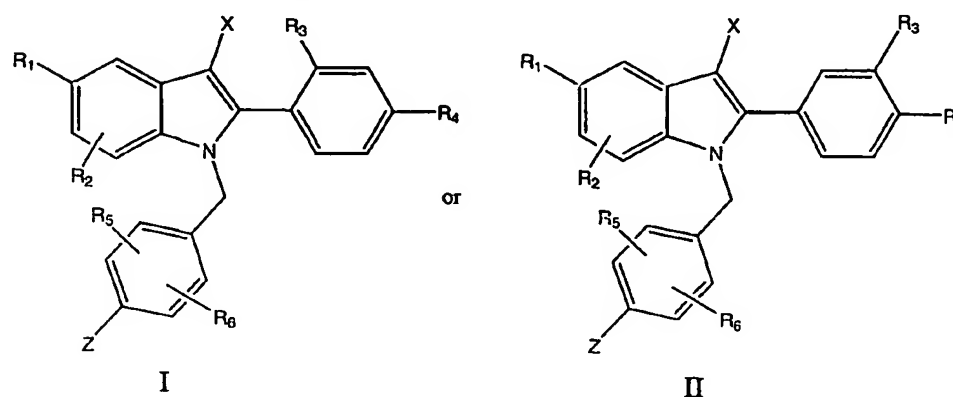
A film coat of White Opadry I (YS-1-18027-A) was applied to the tablets, which
 30 were compressed as follows:

	<u>Dose of TSE-424</u>	<u>tablet weight, mg</u>	<u>mg of film coat applied/tablet</u>
	5 mg	100	6.0
	10 mg	200	8.0
35	20 mg	400	13.0

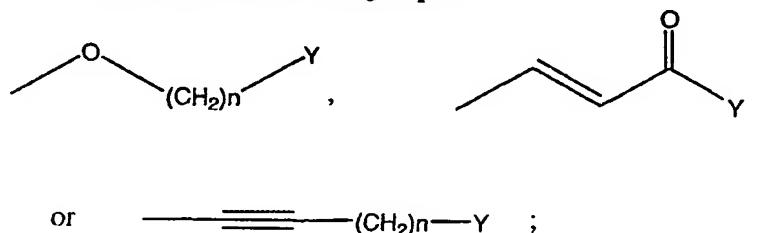
CLAIMS:

1. A method for treatment of bone disorders in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a:

- i) a bisphosphonate, or a pharmaceutically acceptable salt thereof;
- ii) a substituted indole compound of the formulae I or II:



10 wherein Z is a moiety selected from the group of:



wherein:

R_1 is selected from H, OH or the C_1 - C_{12} esters or C_1 - C_{12} alkyl ethers thereof, benzyloxy, or halogen; or C_1 - C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether;

R_2 , R_3 , R_5 and R_6 are independently selected from H, OH or the C_1 - C_{12} esters or C_1 - C_{12} alkyl ethers thereof, halogens, or C_1 - C_4 halogenated ethers, cyano, C_1 - C_6 alkyl, or trifluoromethyl, with the proviso that, when R_1 is H, R_2 is not OH;

R_4 is selected from H, OH or the C_1 - C_{12} esters or C_1 - C_{12} alkyl ethers thereof, halogens, or C_1 - C_4 halogenated ethers, benzyloxy, cyano, C_1 - C_6 alkyl, or trifluoromethyl;

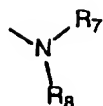
X is selected from H, C_1 - C_6 alkyl, cyano, nitro, trifluoromethyl, halogen;

n is 1, 2 or 3;

- 36 -

Y is selected from:

a) the moiety:



wherein R₇ and R₈ are independently selected from the group of H, C₁-C₆ alkyl, or phenyl optionally substituted by CN, C₁-C₆ alkyl, C₁-C₆ alkoxy (straight chain or branched), halogen, -OH, -CF₃, or -OCF₃; or R₇ and R₈ are combined by -(CH₂)_p-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydroxyl, halo, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄alkylamino, di-(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl and -NO₂;

b) a five-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁-C₄ alkyl)-, -N=, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄acyloxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, -CN-, -CONHR₁, -NH₂, C₁-C₄alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R₁, -NHCOR₁, -CONH(C₁-C₄)alkyl, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, -NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄)alkyl;

c) a six-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁-C₄ alkyl)-, -N=, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₂-C₄acyloxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, -CN, -CONHR₁, -NH₂, C₁-C₄alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R₁, -NHCOR₁, -CONH(C₁-C₄)alkyl, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄)alkyl;

d) a seven-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁-C₄ alkyl)-, -N=, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₂-C₄acyloxy, C₁-C₄alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H-, -CN-, -CONHR₁-, -NH₂, C₁-C₄alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R₁-, -NHCOR₁-, -CONH(C₁-C₄)alkyl, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, -NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or

e) a bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁C₄ alkyl)-, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄acyloxy, C₁-C₄alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H-, -CN-, -CONHR₁-, -NH₂-, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R₁-, -NHCOR₁-, -CONH(C₁-C₄)alkyl, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, -NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄) alkyl; or a pharmaceutically acceptable salt thereof.

and, optionally

iii) one or more estrogens, or a pharmaceutically acceptable salt thereof;

2. The method of Claim 1 wherein in the compound of the formulae I or II: R₁ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, or halogen;

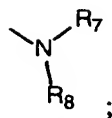
R₂, R₃, R₅, and R₆ are independently selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl; with the proviso that, when R₁ is H, R₂ is not OH;

R₄ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl;

X is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, halogen;

- 38 -

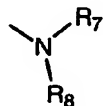
Y is the moiety:



- R₇ and R₈ are selected independently from H, C₁-C₆ alkyl, or combined by -(CH₂)_p-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄alkylamino, di(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂;
- or a pharmaceutically acceptable salt thereof.

3. The method of Claim 2 wherein, in the compound of the formulae I or II, the ring formed by a the combination of R₇ and R₈ by -(CH₂)_p- is selected from aziridine, azetidine, pyrrolidine, piperidine, hexamethyleneamine or heptamethyleneamine.

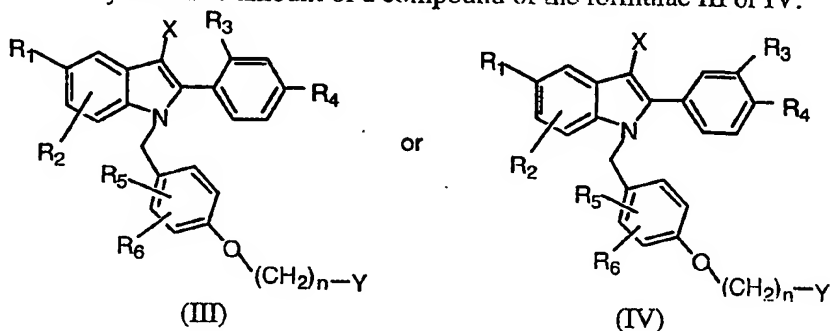
4. The method of Claim 1 utilizing a compound of the formulae I or II, wherein R₁ is OH; R₂ - R₆ are as defined in Claim 1; X is selected from the group of Cl, NO₂, CN, CF₃, or CH₃; and Y is the moiety:



- and R₇ and R₈ are concatenated together as -(CH₂)_r-, wherein r is an integer of from 4 to 6, to form a ring optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄alkylamino, di(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂;
- or a pharmaceutically acceptable salt thereof.

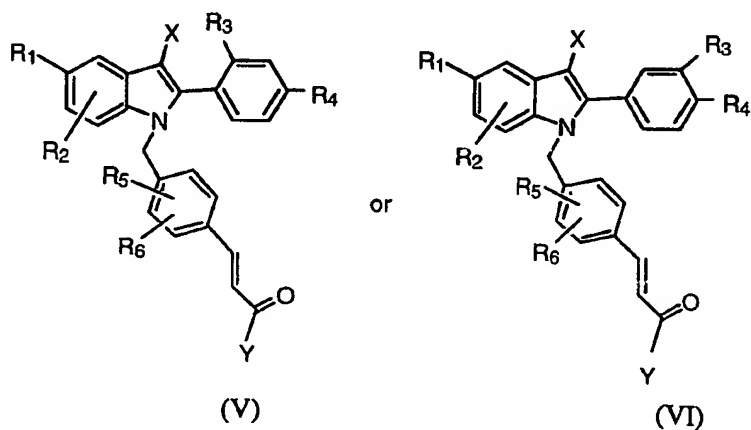
5. A method for treatment of bone disorders in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a bisphosphonate, or a pharmaceutically acceptable salt thereof, and

optionally one or more estrogens, or a pharmaceutically acceptable salt thereof, and a pharmaceutically effective amount of a compound of the formulae III or IV:



5 wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , n , X , and Y are as defined in Claim 1, or a pharmaceutically acceptable salt thereof.

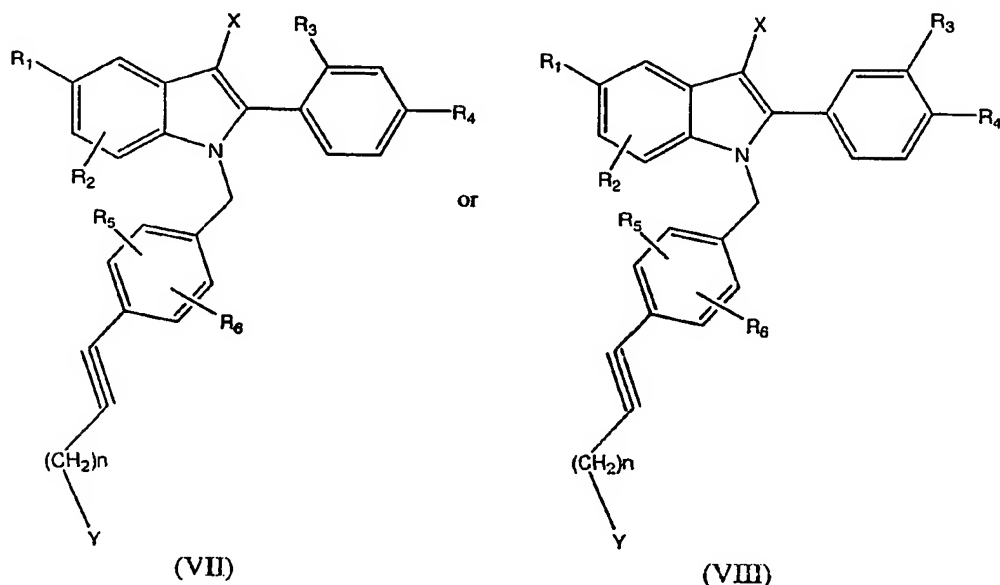
6 A method for treatment of bone disorders in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a bisphosphonate, or a pharmaceutically acceptable salt thereof, and optionally one or more estrogens, or a pharmaceutically acceptable salt thereof, and a pharmaceutically effective amount of a compound of the formulae (V) or (VI):



15 wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , X , and Y are as defined in Claim 1, or a pharmaceutically acceptable salt thereof.

20 7. A method for treatment of bone disorders in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a bisphosphonate, or a pharmaceutically acceptable salt thereof, and

optionally one or more estrogens, or a pharmaceutically acceptable salt thereof, and a pharmaceutically effective amount of a compound of the formulae VII and VIII:



wherein R₁, R₂, R₃, R₄, R₅, R₆, n, X, and Y are as defined in Claim 1, or a pharmaceutically acceptable salt thereof.

8. A method according to Claim 1 in which the compound of formula I or
10 Ia is 1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-
ol, or a pharmaceutically effective salt thereof.

or

2-(4-hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-1H-indol-5-ol,
or a pharmaceutically effective salt thereof.

15

9. A method according to any one of claims 1 to 8 wherein the bisphosphonate is selected from the group of Alendronate, Risedronate, Tiludronate, Ibandronate, Etidronate, Clodronate, Minodronate, Pamidronate, Zoledronate, Incadronate, Olpadronate or Neridronate.

20

10. A method according to any one of claims 1 to 9 wherein the one or more estrogens are selected from the group of estrone, estriol, equilin, estradiene, equilenin, ethinyl estradiol, 17 β -estradiol, 17 α -dihydroequilenin, 17 β -dihydro-

- 41 -

equilenin, 17α -dihydroequilin, 17β -dihydroequilin, menstranol, conjugated estrogenic hormones, equol, enterolactone, or a pharmaceutically acceptable salt thereof.

5 11. A method according to any one of claims 1 to 10 wherein the bone disorder is osteoporosis.

 12. A method according to any one of claims 1 to 10 wherein the bone disorder is Paget's disease.

10 13. A method according to any one of claims 1 to 10 wherein the bone disorder is malignant osteolytic bone disease.

 14. A method according to any one of claims 1 to 10 wherein the bone disorder is bone degradation due to metastases from cancer.

 15. A method for treatment of bone disorders in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of 1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol, or a pharmaceutically effective salt thereof, a pharmaceutically effective amount of a bisphosphonate, or a pharmaceutically effective salt thereof, and optionally one or more estrogens, or a pharmaceutically acceptable salt thereof.

20 16. A method for treatment of bone disorders in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of 2-(4-hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-1H-indol-5-ol, or a pharmaceutically effective salt thereof, a pharmaceutically effective amount of a bisphosphonate or a pharmaceutically acceptable salt thereof, and optionally, one or more estrogens or a pharmaceutically effective salt thereof.

30 17. The method of Claim 15 or Claim 16 wherein the bisphosphonate is selected from the group of Alendronate, Risedronate, Tiludronate, Ibandronate, Etidronate, Clodronate, Minodronate, Pamidronate, Zoledronate, Incadronate, Olpadronate or Neridronate, or a pharmaceutically acceptable salt thereof.

35

- 42 -

18. The method of Claim 15, 16 or Claim 17 wherein the one or more estrogens are conjugated estrogenic hormones.

19. A product comprising a compound of formula I or II as defined in any
5 one of claims 1 to 8 or a pharmaceutically acceptable salt thereof, and a bisphosphonate or a pharmaceutically acceptable salt thereof, and optionally one or more estrogens, or a pharmaceutically acceptable salt thereof for administration as a combined preparation for simultaneous, separate or sequential use in treatment of bone disorders in a mammal.

10 20. A pharmaceutical composition comprising a compound of formula I or II as defined in any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof, and a bisphosphonate or a pharmaceutically acceptable salt thereof, and optionally one or more estrogens, or a pharmaceutically acceptable salt thereof;
15 and a pharmaceutically acceptable carrier.

